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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/419,901 | 10/18/1999 | JENNIFER E. VAN EYK | PTQ-0028 | 2043 |

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| EXAMINER | |
|---|---|
| COOK, LISA V | |
| **ART UNIT** | **PAPER NUMBER** |
| 1641 | |

| NOTIFICATION DATE | DELIVERY MODE |
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| 11/30/2007 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

poreilly@licataandtyrrell.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/419,901 | VAN EYK ET AL. | |
| | Examiner | Art Unit | |
| | Lisa V. Cook | 1641 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-7,16-18,20-28,31,34,35 and 37-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 16-18, 20-28, 31-35 and 37-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Amendment Entry*

1. Applicant's response to the Office Action mailed May 2, 2007 is acknowledged (paper filed 9/4/07). Claims 8-15, 19, 29-30, 32-33, 36, and 42-68 have been canceled. Currently claims 1-7, 16-18, 20-28, 31, 34-35, and 37-41 are pending and under consideration.

2. Objections and/or rejections of record not reiterated below have been withdrawn.

REJECTIONS WITHDRAWN

### *Double Patenting*

3. Double patenting obviousness-type rejection:

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

***Response to Arguments***

Applicant has filed a TD over application #09/115,589. The TD filed 9/4/07 has been approved. Accordingly, the rejections under obviousness double patenting have been withdrawn.

REJECTIONS MAINTAINED

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**I.** Claims 1, 16-18, 20-27, 31 and 34 are rejected under 35 U.S.C.103 (a) as being unpatentable over Lofberg et al. (Archives of Neurology, Vol.52, 12/1995, pages 1210-1214) in view of Solaro et al. (Journal of Molecular Cell Cardiology, Vol.28, pages 217-230, 1996) and Lin et al. (The journal of Biological Chemistry, Vol.271, No.1, 1/5/1996, pages 244-249) and further in view of Han et al. (International Journal of Biochemistry, Vol.24, No.1, 1992, pages 19-28).

Lofberg et al. teach that cardiac TnT, TnI and myosin were evaluated - tissue-specific indicators of muscle damage. In particular, cardiac troponin I (TnI) was a specific marker for myocardial damage. See abstract. TnI is apart of the troponin complex. It prevents contraction in the absence of calcium and calcium binding troponin C (TnC) –muscle damage. See page 1211 1st column. Cardiac TnI proved to be highly specific for myocardial damage. See page 1213.

Lofberg et al. differ from the instant invention in not specifically teaching myofilament protein modification products. The specification has indicated that phosphorylation is a process resulting in myofilament protein modification products. See page 10 lines 10-24 for example.

Solaro et al. teach that myofilament proteins are important in the change of cardiac function associated with ischemia, reperfusion injury, and stunning – muscle damage. See page 227, 1st column–Conclusion. The mechanical state of the myofilament proteins by covalent, non-covalent, and the isoform population are involved in the transition from diastolic to the systolic state. See abstract. The myofilament proteins include actin, TnC, TnI, and Tm. See figure 1 on page 218.

Myofilament phosphorylation is also taught to be important in the interaction of TnI/TnC and relaxation rates due to calcium sensitivity. See page 221 - 1st and 2nd column/figure 3. TnI residue (myofilament protein modification products) phosphorylation has important effects on the interaction of TnI with TnC which can lead to reduced sensitivity of the myofilaments to Ca2+ and increased relaxation rated of the myofilaments. See page 221.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to measure myofilament protein modification products as taught by Solaro et al. in the muscle assessment methods of Lofberg et al. because Solaro et al. taught that TnI residue (myofilament protein modification products) phosphorylation has important effects on the interaction of TnI with TnC which can lead to reduced sensitivity of the myofilaments to Ca2+ and increased relaxation rated of the myofilaments. See page 221. Such altered myofilament functions could lead to cardiac injury, damage and or death. See page 222.

Lofberg et al. in view of Solaro et al. differ from the instant invention in not specifically detecting a chemical adduct of the myofilament protein modification product.

However, Lin et al. teach procedures to measure covalent binding of peptides to cardiac troponin C. Troponin C is disclosed as important in the regulation of contraction in striated muscle. In order to test troponin C's involvement in muscle contraction, a synthetic peptide or biotin was coupled to troponin to produce covalent adducts.

These adducts were evaluated for activity in TnC-extracted myofibrils. See abstract and page 244-2nd column 3rd paragraph and figure 4. In some instances the peptides were reversible coupled to cTnC. See figure 2.

It was demonstrated that covalent modification of cTnC (C81) with either the peptide or biotin resulted in significant inhibition of activity. See page 248 1st column –Discussion. This data is important to the mechanism of action of hydrophobic anti-CaM drugs that sensitize muscle to $Ca^{2+}$ and potentiate rather than inhibit muscle contraction. A drug with Met-81 would inhibit rather than enhance the function of cTnC. See page 248, 2nd column.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to measure myofilament chemical adducts as taught by Lin et al. in the detection methods of Lofberg et al. in view of Solaro et al. because Lin et al. taught that chemical adduct modifications exhibited inhibition of myofibril activity. Specifically, the covalent modification of cTnC (C81) with either the peptide or biotin resulted in significant inhibition of activity. See page 248 1st column –Discussion. This data (myofilament chemical adduct modification) is important to the mechanism of action of drug development and utility in muscle contraction (damage/function). See page 248, 2nd column.

Lofberg et al. in view of Solaro et al. and Lin et al. are silent with respect to the myofilament protein modification product being a post-translational modification.

Han et al. teach that post-translational modification involve the making or breaking of covalent bonds. Post-translational modifications are varied. See abstract, page 19-1st column and page 21, for example.

Han et al. further disclose that numerous post-translational modification are recognized in a wide variety of cell types. The covalent changes play several roles in protein-ligand interaction, subcellular organization, assembly of bimolecular complexes, regulation of the catalytic activity, and/or protein turnover. It is well established that each modification severs a useful role..... See page 25-Discussion.

Lofberg et al. in view of Solaro et al. and Lin et al. disclose the claimed method except for specifically indicating that the myofilament modification occurs as a post-translational modification. Han et al. disclose that it is known in the art that protein modification occurs post-translationally and include phosphorylation. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to detect post-translational modifications, in order to evaluate protein-ligand interaction, subcellular organization, assembly of bimolecular complexes, regulation of the catalytic activity, and/or protein turnover as they relate to muscle damage. See Han et al. page 25-Discussion.

**II.** Claims 2-7, 28, 34-35, 38 and 40-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lofberg et al. (Archives of Neurology, Vol.52, 12/1995, pages 1210-12140) in view of Solaro et al. (Journal of Molecular Cell Cardiology, Vol.28, pages 217-230, 1996) and Lin et al. (The journal of Biological Chemistry, Vol.271, No.1, 1/5/1996, pages 244-249) and further in view of Han et al. (International Journal of Biochemistry, Vol.24, No.1, 1992, pages 19-28) as applied to claims 1, 16-18, 20-27, and 34 above, and further in view of Wicks et al. (US patent #5,834,220).

Lofberg et al. in view of Solaro et al. and Lin et al. further in view of Han et al. are set forth above.

Lofberg et al. in view of Solaro et al. and Lin et al. further in view of Han et al. differ from the instant invention in not teaching an quantitative (amount) assessment of muscle damage further employing two different myofilament protein modification products.

However, Wicks et al. teach method for assaying for cardiac troponin I along with troponoin C. See abstract. The process and test system provide rapid and specific measurements of troponin I and is highly suitable for confirming the diagnosis of myocardial damage (reading on muscle damage).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to measure two different myofilament product degradation products (troponin I and troponin C) in muscle damage as taught by Wicks et al. in the method of Lofberg et al. in view of Solaro et al. and Lin et al. further in view of Han et al. because Wicks et al. taught that Troponin I is one of three subunits of the troponin complex. The other two subunits (designated T and C) are also immobilized on the thin myofilaments along with troponin I in both cardiac and skeletal muscle tissue. Column 1., lines 23-40. The utility of both troponin I and troponin C allowed for further distinction between cardiac muscle damage or skeletal muscles damage. See column 2, lines 37-49.

One having ordinary skill in the art would have been motivated to do this to acquire the enhanced sensitivity and ability to reduce false positives while providing more data sets for analysis, wherein accurate and precise detection is available.

**III.** Claims 37 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lofberg et al. (Archives of Neurology, Vol.52, 12/1995, pages 1210-12140) in view of Solaro et al. (Journal of Molecular Cell Cardiology, Vol.28, pages 217-230, 1996) and Lin et al. (The journal of Biological Chemistry, Vol.271, No.1, 1/5/1996, pages 244-249) and further in view of Han et al. (International Journal of Biochemistry, Vol.24, No.1, 1992, pages 19-28) and Wicks et al. (US patent #5,834,220) as applied to claims 2-7, 28, 34-35, 38 and 40-41 above, and further in view of Jideama et al. (The Journal of Biological Chemistry, Vol.271, No.38, 9/20/96, pages 23277-23283).

Please see Lofberg et al. in view of Solaro et al. and Lin et al. further in view of Han et al. and Wicks et al. as set forth above.

Lofberg et al. in view of Solaro et al. and Lin et al. further in view of Han et al. and Wicks et al. differ from the instant invention in not teaching an assessment of the myofilament proteins as a change with time as required in claims 37 and 39.

However, Jideama et al. teach methods to analyze phosphorylation states and properties for myofilament proteins. These myofilament proteins include troponin I and troponin T. The proteins were measured over time (5-120min) –assessing a change with time. Jideama et al found that the phosphorylation state and properties of the myofilament proteins were time dependent relating to phosphorylation extent, substrate affinity, and inhibitions. See page 23278 2$^{nd}$ column –Results through page 23279 and figure 2.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to measure myofilament product degradation products involving phosphorylation states as taught by Jideama et al. in the method of Lofberg et al. in view of Solaro et al. and Lin et al. further in view of Han et al. and Wicks et al. because Jideama et al. taught that the phosphorylation state and properties of myofilament proteins were time dependent relating to phosphorylation extent, substrate affinity, and inhibitions. See page 23278 2nd column –Results through page 23279 and figure 2.

One of skill in the art would have been motivated to measure myofilament products over time in order to evaluate and account for the changes exhibited in phosphorylation extent, substrate affinity, and inhibitions.

***Response to Arguments***

5. Applicants contend that while Lofber discloses the use of various antibodies, detectable labels and markers to detect fragments of myosin heavy-chain, troponin I and troponin T; for the purpose of assaying acute muscle damage, it does not detect the presence of the any of the myofilament protein modification products claimed. This argument was carefully considered but not found persuasive because Lofber has been cited in combination with Solaro et al., Lin et al., and Han et al. with or without Wicks et al. and/or Jideama et al. in order to make the invention obvious.

More specifically, Solaro et al. taught that TnI residue (myofilament protein modification products) phosphorylation has important effects on the interaction of TnI with TnC which can lead to reduced sensitivity of the myofilaments to Ca2+ and increased relaxation rated of the myofilaments. See page 221. Such altered myofilament functions could lead to cardiac injury, damage and or death. See page 222. Therefore it is deemed obvious to measure post translational modification products of TnI in muscle damage.

With respect to the modification being a chemical adducts, Lin et al. has been cited to exemplify covalent modification of cTnC (C81) with either the peptide or biotin resulted in significant inhibition of activity. See page 248 1st column –Discussion. This data is important to the mechanism of action of hydrophobic anti-CaM drugs that sensitize muscle to $Ca^{2+}$ and potentiate rather than inhibit muscle contraction. A drug with Met-81 would inhibit rather than enhance the function of cTnC. See page 248, 2nd column.

While a deficiency in a reference may overcome a rejection under 35 USC 103, a reference lacks a teaching for which other references are relied. In re Lyons, 364 F.2d 1005, 150 USPQ 741, 746 (CCPA 1966).

Applicant argues that the combination of references provide no teaching or suggestion of all the claim limitations and no reasonable expectation of success. This argument was carefully considered but not found persuasive because KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision Ex parte Smith, ---USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396).

In this case, the cited prior art has demonstrated that the recited markers (i.e. troponin I, troponin T, and troponin C) are myofilament proteins involved in muscle damage. See Lofber et al. in view of Solaro et al. The prior art also teaches that chemical adducts of the markers are involved in muscle function (contraction). See Lin et al. While, Han et al. demonstrates that phosphorylation products involving the recited markers are known and effect covalent bonds (reading on chemical adduct modifications). Therefore, it would have been prima facie obvious to one of ordinary skill in the art to measure the modification products instantly claimed in muscle damage. Absent evidence to the contrary, the modification products taught by the prior art are the same as those of the instant method. Thus the claims would have been obvious because the substitution of one known element (i.e. troponin I, troponin T, and troponin C) for another (i.e. modified troponin I, troponin T, and troponin C) would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Since the art discloses that they are all involved in muscle function and/or damage.

6. For reasons aforementioned, no claims are allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 – Central Fax number is (571) 273-8300, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see httpr//pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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